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EXAMINER

SZNAIDMAN, MARCOS L

ART UNIT

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1611

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/594,850	Applicant(s) ROBBINS ET AL.	
	Examiner MARCOS SZNAIDMAN	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 258-278 is/are pending in the application.
- 4a) Of the above claim(s) 262 and 263 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 258-261 and 264-267 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3 pages / 02/07/08</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to applicant's reply filed on February 7, 2008.

Election/Restrictions

Applicant's election with traverse of a composition comprising: i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin) in the reply filed on February 7, 2008 is acknowledged. The traversal is on the ground(s) that "the general inventive concept of the pending claims is the beneficial effects upon cancer patients when the variously recited drugs are administered". This is not found persuasive because the second species has a third component that would require compounds that are not included in the first species, so it would require different search criteria than the first species and do not relate to a general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 258-278 are currently pending and are the subject of this office action.

Claims 262-263 and 268-278 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 7, 2008.

Claims 258-261 and 264-267 are presently under examination.

Priority

The present application is a 371 of PCT/US05/11046 filed on 04/01/2005, and claims priority to provisional applications No. 60/625,479 filed on 11/04/2004; No. 60/558,889 filed on 04/02/2004; and No. 60/658,745 filed on 03/04/2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 258-261 and 264-267 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating colorectal cancer and breast cancer, with a mixture comprising: i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin); does not reasonably provide enablement for treating every type of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without

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undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

- 1- the quantity of experimentation necessary,
- 2- the amount of direction or guidance provided,
- 3- the presence or absence of working examples,
- 4- the nature of the invention,
- 5- the state of the prior art,
- 6- the relative skill of those in the art,
- 7- the predictability of the art, and
- 8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

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1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of treating cancer in a subject in need thereof comprising administering to the subject a mixture comprising : i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved" and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable); *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian vaccine was uncertain). As illustrative of the state of the art, the examiner cites Gura et.

al. (Science, 1997, 278:1041-1042) and Johnson et. al. (British Journal of Cancer, 2001, 84:1424-1431).

Gura et. al., cited for evidentiary purposes, teaches that researches face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousand of drugs have shown activity in either cell or animal models, but only 39 have actually been shown useful for chemotherapy (see page 1041, first and second paragraph). Also, with regard to unpredictability, Johnson et al., also cited for evidentiary purposes, teach that the in vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer (see Results on page 1426). *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

Prior art predicts the use of the claimed mixture in colorectal (Hurwitz et. al., Proceedings of the Annual Meeting of the American Society of Clinical Oncology, May 2003, cited by applicant, see title and abstract) and breast cancer (Carlsson et. al., The

Cancer Journal (1997), 10:266-273, cited by applicant, see title, abstract and first paragraph of the introduction; and Anon, CAS accession No. 2003:518, corresponding to Clinical Breast Cancer (2003), 3:375-377, see title and abstract).

2. The breadth of the claims

Claims 258-261 and 264-267 are very broad in terms of the type of diseases being treated: all types of cancer, and claim 258 is very broad regarding the number of compounds that can be used to treat any type of cancer.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides cell data for the inhibition of human colon carcinoma. There is no data for any other type of cancer either *in vitro* or *in vivo*. The specification does not provide further guidance for determining the particular administration regimes (e.g. dosages, timing, administration routes, etc.) necessary to treat all of the various cancer types claimed.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that a mixture comprising : i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin) could be predictably used

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as treatment for all cancers (except for colorectal and breast cancer). Since there is only precedent in the literature for the treatment of colorectal and breast cancer with the above described mixture, how is the skilled physician supposed to know what type of dose regimen of: i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin) to use for each of the pathologically different cancers?

Determining if a mixture of: i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin) will treat any particular cancerous disease state (except for colorectal and breast cancer) would require formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 258-261 and 264-267 do not comply with the scope of enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 258-261 and 264-267 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hurwitz et. al. (Proceedings of the Annual Meeting of the American Society of Clinical Oncology, May 2003, cited by applicant, see title and abstract),

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Carlsson et. al. (The Cancer Journal (1997), 10:266-273, cited by applicant, and Anon (CAS accession No. 2003:518, corresponding to Clinical Breast Cancer (2003), 3:375-377).

Claims 258-261 and 264-267 recite a method of treating a patient with a cancerous tumor, the method comprising co-administering to the patient: : i) 5-fluorouracil (5-FU), ii) 5,10-methylene tetrahydrofolate, and iii) Bevacizumab (Avastin).

Hurwitz et. al. teach a method of treating colorectal cancer with a mixture comprising: i) 5-fluorouracil (5-FU), ii) leucovorin (leucovorin is metabolized in vivo to 5,10-methylene tetrahydrofolate as evidenced by Carlsson et. al., see first paragraph of the introduction) , iii) Bevacizumab (Avastin) and iv) irinotecan.

Carlsson et. al. teach a method of treating breast cancer with a combination of: : i) 5-fluorouracil (5-FU), and ii) 5,10-methylene tetrahydrofolate (see title, abstract and first paragraph of the introduction). Carlsson et. al. do not teach treating breast cancer with bevacizumab. However, Anon teaches a method of treating breast cancer with a mixture comprising bevacizumab (see title and abstract).

At the time of the invention it would have been prima facie obvious for a person skilled in the art to treat colorectal or breast cancer with the above combination, based on the teachings of the prior art, thus resulting in the practice of claims 258-261 and 264-267 with a reasonable expectation of success.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLS
March 19, 2008

/Michael P Woodward/
Supervisory Patent Examiner, Art
Unit 1615